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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,035	10/07/2003	Mariann Pavone-Gyongyosi	ARTHP118US	5279

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
09/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/680,035	PAVONE-GYONGYOSI ET AL.	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/20/2004, 12/17/2004, 04/16/2009, 06/03/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 22-30, the caspase inhibitor species Ac-YVAD-CMK and the R-Lys-X species SEQ ID NO: 64, in the reply filed on 08/16/2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. The elected species were searched and prior art was found. Therefore, the search was not extended in accordance with MPEP § 803.02.

Information Disclosure Statement

2. The information disclosure statements filed 02/20/2004 and 04/16/2009 fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the non-patent literature references do not include titles. The information referred to in the lined-through citations has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 22-27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the definition for variables R and X in the formula R-Lys-X.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 22-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP § 2163 states that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics.

7. Claims 22-28 are drawn to a method of making a hemocompatibly coated medical product comprising coating the surface of the product with at least one caspase inhibitor and/or at least one compound of formula R-Lys-X. Claims 29 and 30 are drawn to the coated medical product.

8. The USPTO provides claim terms with broadest reasonable interpretation in light of the specification. The scope of the claim terms "medical product," "caspase inhibitor" and compound of formula R-Lys-X" is interpreted as follows.

9. The specification lists the following as examples of medical products on p. 3, lns 25-32: artificial hearts, heart parts, lungs, arteries, veins, aortas, heart valves, corpse veins, valves, containers, bags, cans, needles, catheters, artificial parts for the cardiovascular system and the extracorporeal circulation, surgical implants such as stents or catheters and devices for analytical purposes such as test tubes, titer plates, micro titer plates, well plates, analytical chips or material for chromatography such as gels, silica gels, columns, alumina, and sepharose gels. The scope of the claim term includes medical products intended for both *in vivo* and *in* vitro use. The specification states that stents are the preferred medical product (p. 4, lns 1-2, Examples) and claim 30 is limited to this embodiment.

10. Caspases are the key effector molecules of apoptosis, although some are involved in the activation of cytokines. Inhibition of caspases by viral and cellular proteins as well as by synthetic molecules designed from the recognition sequences of the caspases is well-known in the art (see Ekert et al. "Caspase Inhibitors" *Cell Death and Differentiation*, **1999**, *6*, 1081-1086). The instant specification lists numerous known caspase inhibitors. Thus, the scope of the claim term encompasses both small molecule peptide inhibitors as well as viral and cellular proteins. The specification identifies Ac-YVAD-cmk as a preferred embodiment. The example in the specification demonstrates that the intracoronary administration of Ac-YVAD-cmk before stenting decreases neointimal hyperplasia. This work was also published in the prior art (Gyöngyösi et al. "Inhibition of interleukin-1β convertase is associated with decrease of neointimal hyperplasia after coronary artery stenting in pigs," *Molecular and Cellular Biochemistry* **249:** 39–43, 2003). Stents coated with Ac-YVAD-cmk to treat acute myocardial infarction are also known in the art (Bell US 2004/0219147) however the instant specification

does not include any examples of stents or other medical products coated with Ac-YVAD-cmk or any other caspase inhibitor.

11. The claim term "compound of formula R-Lys-X" is indefinite, as noted above, because claims 22-27, 29 and 30 fail to define the variables R and X. The definition in the specification and in claim 28 states that X is hydroxyl, amino, monoalkyl or dialkylamino, alkoxy, amino acid or a peptide with 1-10 amino acids, and that R is hydrogen, acyl, acetyl, amino acid or a peptide with 2-70 amino acids. Thus, the scope of R-Lys-X includes lysine and peptides from 2 to 80 amino acids in length containing lysine at any one of positions 1-11. For the 80mer peptide alone the genus includes approximately 20^{80} or 1.2×10^{104} different peptide sequences. The instant specification identifies alpha-melanocyte stimulating hormone (alpha-MSH) as a preferred embodiment (p. 8, ln 1) but does not present a medical device coated with alpha-MSH.

12. In summary, the scope of the claims with respect to the terms medical product," "caspase inhibitor" and compound of formula R-Lys-X" is extremely broad. The specification states that the purpose of the invention is to provide medical products which reduce the risk of restenosis and methods for manufacturing said coated medical products.

13. No embodiments of the invention of claims 22-30 were reduced to practice at the time of filing. The example pertaining to the use of Ac-YVAD-cmk involved the administration of the caspase inhibitor prior to stenting did not involve the use or manufacture of a stent coated with Ac-YVAD-cmk or any other caspase inhibitor or compound of formula R-Lys-X.

14. In the absence of a reduction to practice of a representative number of species, the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by

functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. To meet this requirement in the instant case, the specification must describe the structural, physical and/or chemical properties of a caspase inhibitor and compounds of formula R-Lys-X that lead to the claimed function of hemocompatibility and the intended function of restenosis inhibition. The instant specification fails to provide guidance on how to identify compounds suitable for this purpose. It does not provide a structure-function correlation for compounds of formula R-Lys-X, nor does it address whether caspase inhibitors other than Ac-YVAD-cmk can mitigate restenosis. Furthermore, the specification does not clarify the relationship between the caspase inhibitor and the compound of R-Lys-X. It is not clear whether R-Lys-X compounds are selected for their ability to inhibit caspases or if they provide some other function that contributes to the overall effect on restenosis and hemocompatibility.

15. In conclusion, for these reasons, the skilled artisan would not reasonably conclude that the inventor(s), at the time the application was filed, had possession of the full scope of the claimed invention.

16. Claims 22-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use and manufacture of a stent coated with Ac-YVAD-cmk and the *in vitro* use and manufacture of a tissue culture or 96-well plate coated with alpha-MSH, does not reasonably provide enablement for the use of medical products coated with other caspase inhibitors or coated with compounds of formula R-Lys-X. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

17. To comply with the enablement requirements of 35 U.S.C. §112, first paragraph, a specification must adequately teach how to make and how to use a claimed invention throughout its scope, without undue experimentation. *Plant Genetic Systems N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003). There are a variety of factors which may be considered in determining whether a disclosure would require undue experimentation. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

18. The nature and breadth of the claims and the absence of working examples is addressed above. In summary, the scope of the claims with respect to the terms medical product," "caspase inhibitor" and compound of formula R-Lys-X" is extremely broad. Despite this breadth, the specification fails to disclose a single working example of a medical product coated with a caspase inhibitor and/or compound of formula R-Lys-X. The specification states that the purpose of the invention is to provide medical products which reduce the risk of restenosis and methods for manufacturing said coated medical products

19. The instant claims fail to meet the enablement requirements of 35 U.S.C. §112, first paragraph, on the following grounds: 1) the specification is not fully enabled for the intended use of inhibiting restenosis, 2) the specification is not enabled for use of the full scope of compounds

of formula R-Lys-X, and 3) the specification is not enabled for the combined use of the caspase inhibitor and the compound of formula R-Lys-X.

20. With respect to the intended use of restenosis inhibition, there is a high level of unpredictability in the art. Slavin et al. ("Drug-eluting Stents: Preventing Restenosis," *Cardiology in Review*, **2007**, *15*, 1-12) outline the state of the field: "Overshadowing the early success of angioplasty was the high rate of angiographic restenosis and recurrent symptoms at 6 months. The use of stents reduced the incidence of restenosis; however, the rise in the number of patients undergoing percutaneous interventions produced a new problem of restenosis occurring within the stent: in-stent restenosis (ISR). Mechanical approaches, including directional and rotational atherectomy and systemic pharmacotherapy, have failed to demonstrate a reduction in ISR in randomized clinical trials. Intravascular brachytherapy is currently the only approved therapy for ISR, although this treatment has numerous unresolved questions and is not effective in a large percent of patients. Drug eluting stents have reduced the incidence of restenosis by providing localized therapy to the targeted lesion without systemic toxicity." Slavin et al. teach that drug-eluting stents come in two types: stents coated directly with the drug and stents coated with polymer layers that are subsequently loaded with the drug (p. 3, col 2). According to Slavin et al. the choice of polymer is complicated: "the majority of polymers used for stent coating have introduced a substantial amount of inflammation in experimental models. The major concerns that arise from the use of polymers include chronic inflammation specifically after the elution is complete, direct local toxicity to the vascular tissue, polymer incompatibility with circulating humoral factors, and polymer breakdown and erosion." Slavin et al. also teach

that although many agents were tested in the preclinical analysis, only two have demonstrated success, sirolimus and paclitaxel (p. 3, col 2).

21. The instant specification fails to provide guidance necessary to compensate for this high level of unpredictability in the art. The specification lists numerous polymers as suitable for medical product coating with addressing the important therapeutic factors identified by Slavin et al. The skilled artisan would not know how to choose a polymer from amongst those listed in the specification that delivers antirestenotic therapy over an appropriate time course and in the process remains biologically inert, tolerates mechanical stress, and is not thrombogenic. Likewise, the specification lists numerous caspase inhibitors but does not provide guidance on how to select a caspase inhibitor that would be effective at inhibiting restenosis. The data presented on Ac-YVAD-cmk is not representative of the full scope of caspase inhibitors because there are numerous caspase families each with different functions. Furthermore, the drugs used in the art, sirolimus and paclitaxel, are not caspase inhibitors. Finally, the specification provides no guidance on how to use compounds of formula R-Lys-X to inhibit restenosis, including the preferred embodiment alpha-MSH.

22. Next, with respect to the scope of the claim term "compounds of formula R-Lys-X" it is noted that this claim element encompasses a countless number of peptide sequences. Given that protein sequence is unpredictability tied to function, the genus R-Lys-X must include species of diverse function, some of which may be useful for the intended purpose of restenosis inhibition. The specification however fails to provide guidance to identify which structural elements are critical for this function. In addition, the specification fails to provide guidance on how to use

compounds of R-Lys-X that have no impact on restenosis but which likely constitute a large portion of the genus.

23. Finally, the specification offers no guidance on how to use the caspase inhibitors and compounds of formula R-Lys-X together. The specification does not describe what the respective roles of these compounds is on the medical product. For example, it is not clear if both compounds function as caspase inhibitors or if the R-Lys-X compound has an addition complementary role, and if so, what that role may be. The specification does not describe how to optimize the pairing of the compounds to maximize their usefulness. Furthermore, the specification does not describe how to manufacture a medical product with a coating containing two active agents. It is not clear how the agents will affect each other in the coating and if steps are required to optimize the usefulness of the two agents in combination.

24. Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if one of the claimed medical products would be effective at inhibiting restenosis, or finding an alternative use for the product. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation. Therefore, in view of the *Wands* factors, the claims appear to require undue experimentation to use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

26. Claims 29 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by Bell (US 2004/0219147). Bell teaches a stent comprising a coating that contains an antiapotopic compound, wherein the antiapotopic compound is a caspase inhibitor. Bell teaches that the caspase inhibitor is selected from the group consisting of z-VAD-DCB, z-DEVD-fmk, gene p35, z-VAD-fmk, Z-Asp-DCB, MMPSI, Z-IETD-fmk, z-LEHD-fmk, Ac-DEVD-cmk, acetyl-DEVD-CHO, BAF, BocD-fmk, Y-VAD-cmk, YVAD-aldehyde, YVAD, DEVD-aldehyde, DEVD, Ac-Try-Val-Ala-Asp-aldehyde, crmA, Ac-YVAD-cmk, Ac-YVAD-fmk, CPP, z-DEVD-fmk and angiotensin-converting enzyme (ACE) inhibitors (claim 68).

27. Claims 22-25, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Chluba et al. ("Peptide Hormone Covalently Bound to Polyelectrolytes and Embedded into Multilayer Architectures Conserving Full Biological Activity," *Biomacromolecules*, **2001**, *2*, 800-805). Chluba et al. teach a method of making a medical product comprising the steps of a) providing the surface of a medical product, b) coating the surface with a biodegradable polymer, b') coating the layer containing the biodegradable polymer with a composition containing a compound of formula R-Lys-X, the elected species α-MSH, and c) coating the layer containing α-MSH with a biodegradable polymer (p. 801, col 1).

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. Claims 22, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Bell (US 2004/0219147). Bell teaches a stent comprising a coating that contains an antiapotopic compound, wherein the antiapotopic compound is a caspase inhibitor. Bell teaches that the caspase inhibitor is selected from the group consisting of z-VAD-DCB, z-DEVD-fmk, gene p35, z-VAD-fmk, Z-Asp-DCB, MMPSI, Z-IETD-fmk, z-LEHD-fmk, Ac-DEVD-cmk, acetyl-DEVD-CHO, BAF, BocD-fmk, Y-VAD-cmk, YVAD-aldehyde, YVAD, DEVD-aldehyde, DEVD, Ac-Try-Val-Ala-Asp-aldehyde, crmA, Ac-YVAD-cmk, Ac-YVAD-fmk, CPP, z-DEVD-fmk and angiotensin-converting enzyme (ACE) inhibitors. It would have been obvious to make the stent coated with a caspase inhibitor taught by Bell by a) providing the stent, and b) coating it with the caspase inhibitor. With respect to claim 26, it would have been obvious to combine the caspase inhibitors, satisfying the requirement for additional agents.

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 8:30 A.M. to 4:30 P.M.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb